08/690775

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT		ATTY. DOCKET NO.
08/690,775	08/01/96	FELDMANN	M	KIR92-01A4

EXAMINER	
GAMBEL, P	
ART UNIT	**PAPER NUMBER**
1806	10

18N2/1209

DAVID E BROOK
HAMILTON BROOK SMITH & REYNOLDS
TWO MILITIA DRIVE
LEXINGTON MA 02173-4799

DATE MAILED: 12/09/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 9/8/97

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1-3, 5-31 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 1-3, 5-31 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

DETAILED ACTION

1. Applicant's amendment, filed 9/8/97 (Paper No. 8), is acknowledged.
Claims 4 has been canceled.
Claims 1-3 and 5-31 have been amended.

Claims 1-3 and 5-31 are pending and being acted upon presently.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Office Action.
This Office Action will be in response to applicant's arguments, filed 9/8/97 (Paper No. 8).
The rejections of record can be found in the previous Office Action (Paper No. 6).

3. Applicant disagrees with the examiner's position on applicant's claim for priority for the instant application set forth in Paper No. 6; however, applicant asserts that the examiner's observations is believed to be moot in light of the amendment to the claims. However, applicant did not point and provide documentary support for the priority of the instant claims, as amended. Therefore, applicant has not made it clear what is the priority date which is being relied upon. Priority USSN 08/403,785 was not available to the examiner at this time, therefore the examiner could not determined what the filing date of the instant claims as amended. Again, applicant is invited to point out and provide documentary support for the priority of the instant claims. The examiner apologizes for any inconvenience to applicant in examiner's inability to obtain USSN 08/403,785 at this time to verify applicant's priority date for the instant claims. Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

4. The corrected drawings have been received on 9/8/97 (Paper No. 9). These drawings are acceptable.

5. The specification is objected to and claims 1-3, 5-9 and 31 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention to treat any autoimmune or inflammatory disease encompassed by the claimed methods for the reasons of record set forth in the last Office Action (Paper No. 6).

As pointed out in the last Office Action; although in vitro experimental studies and animal models validate concepts based on studies of human disease, such studies are limited to the "acute" as opposed to "chronic" nature of the disease. In vitro assays are conducted under controlled conditions which do not necessarily reflect the complexity of in vivo conditions. In animal models, the onset of inflammation is rapid with an aggressive destructive process, whereas in humans the disease progresses more slowly, often with natural periods of disease exacerbation and remission. Often the antagonist and the stimulus/insult are given at the same time. Immunosuppression is much easier to achieve under such controlled conditions that experienced in the human immunoregulatory diseases such as the acute and chronic immune diseases, autoimmune diseases, inflammatory diseases and neurodegenerative diseases targeted by the claimed invention. In human diseases, patients are treated generally after the onset of disease and not prior to disease.

Natanson et al. (Ann Int Med., 1994) teach that anti-TNF was not beneficial in sepsis and septic shock and that targeting TNF could be harmful (see Anticytokine Therapies).

Therefore, it is not clear that the skilled artisan could predict the efficacy of targeting any TNF-mediated disease or inflammatory disease with any TNF specific antibody and methotrexate. It is important to note that there are distinct differences in the cytokine requirements for particular types of inflammation Applicant has not provided sufficient information or nexus information a priori that establishes the efficacy of the claimed invention for the treatment of any TNF-mediated disease by targeting any TNF. The specification does not teach how to extrapolate data obtained from anti-TNFα and methotrexate on arthritis to the development of effective in vivo human therapeutic methods and compositions for any TNF-mediated diseases, commensurate in scope with the claimed invention.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective anti-inflammatory therapies with anti-cytokine therapy commensurate in scope with the claimed methods and compositions, undue experimentation would be required to practice the claimed methods and compositions with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and compositions and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for inhibiting any autoimmune or inflammatory disease.

Applicant's arguments, filed 9/8/97 (Paper No. 8), have been fully considered but are not found convincing. Applicant asserts that the scientific or technical basis for the examiner's conclusion or beliefs has not been provided. Applicant relies upon the teaching of the specification that TNF-mediated disease can be treated in an individual by co-administering methotrexate and a TNF antagonist to the individual in therapeutically effective amounts, and in turn, relies upon the disclosure of numerous diseases (pages 8-10) and TNF antagonists (pages 12-35). Applicant has exemplified the claimed methods using anti-TNFα antibody cA2 in patients with active rheumatoid arthritis (Examples 1-3) and applicant has extrapolated from this example to the breadth of TNF-mediated diseases and TNF antagonists known to mediated by TNF alpha. Applicant relies upon Le et al. in U.S. Patent No. 5,656,272 to support treating Crohn's disease.

Although applicant asserts that the position that the targeted diseases differ from one another in their cytokine requirements is irrelevant; this is a critical point as it has been art known that antagonizing a particular cytokine such as TNF may be beneficial in certain diseases, targeting the same cytokine in different inflammatory conditions would not lead to any alleviation of symptoms or disease.

Although applicant asserts that the examiner does not apparently dispute the question that the targeted diseases are characterized by TNF alpha; it has been known that a number of inflammatory mediators including TNF alpha may be associated with a number of inflammatory diseases, but treating a disease via a particular mediator is not necessarily predictive from one disease to another.

Although applicant asserts that the examiner has ignored the clinical evidence of record, the examiner has addressed the scope of targeted diseases based upon limited examples (rheumatoid arthritis, Crohn's disease).

Although applicant asserts that amending the claims has obviated the limitations indicated by Natanson et al. (Ann. Int. Med., 1994); claims 1-3, 5-9 and 31 still read on treating on any number of inflammatory diseases, including sepsis and cachexia.

Applicant's arguments have not been found persuasive on the scope of autoimmune and inflammatory diseases, encompassed by the claimed invention.

6. Upon reconsideration of applicant's arguments, filed 9/8/97 (Paper No. 8); the previous deposit requirements under 35 U.S.C. § 112, first paragraph, have been obviated by the disclosure in U.S. Patent No. 5,656,272, which discloses the entire sequence of the chimeric anti-TNFα antibody cA2.

7. Upon reconsideration of applicant's amended claims and arguments, filed 9/8/97 (Paper No. 8); the previous rejections as they would apply to the instant claims under 35 U.S.C. § 112, first and second paragraphs, in the recitation of "tumor necrosis factor-mediated disease", TNF "antagonist", "binds to the epitope of cA2" have been withdrawn.

8. Upon reconsideration of applicant's amended claims and arguments, filed 9/8/97 (Paper No. 8); the previous rejections as they would apply to the instant claims under 35 U.S.C. § 112, second paragraph, have been withdrawn.

9. Applicant's arguments, filed 9/8/97 (Paper No. 8), concerning the prior art of record have been rendered moot in view of the New Grounds of Rejection set forth below.

Applicant has argued that none of the references alone or in combination teach or suggests with a reasonable expectation of success, coadministration of methotrexate and anti-TNFα antibody or other TNFα-specific antagonists to treat an individual for treating rheumatoid arthritis, Crohn's disease or other autoimmune or inflammatory diseases. To make the position of record clearer that combination therapy including TNFα-specific antagonists in combination with art-recognized methotrexate therapy would have been obvious to one of ordinary skill in the art at the time the invention was made with an expectation of success, New Grounds of Rejection have been applied below.

It is acknowledged that applicant asserts the unexpected result that combination therapy with methotrexate and anti-TNFα antibody produced a rapid and sustained reduction in the signs and symptoms of the treated autoimmune disease, namely rheumatoid arthritis (Example 2). Applicant asserts that the combination of methotrexate and anti-TNFα produced markedly superior results to that the results obtained with each agent alone, particularly at low doses of methotrexate. Applicant also asserts that significant improvement of the combination therapy was observed even in comparison to where optimal dosages of anti-TNFα antibody were administered alone (Example 1). Applicant states that is now well settled that significant improvements can rebut a prima facie case of obviousness. See In re Kollman, 201 USPQ 193 (CCPA 1979) and MPEP 716.02.

In contrast to applicant's assertions with respect to Example 2; page 66, paragraph 3 of the instant specification discloses that: the results of the study indicate that treatment with cA2 as adjunctive and/or concomitant therapy to methotrexate therapy is effective in the reduction of the signs and symptoms of rheumatoid arthritis in patients whose disease is incompletely controlled by methotrexate. Moreover, the clinical response achieved by this approach can be sustained for more than 12 weeks after a single treatment. Accordingly, the results of this study indicate that treatment with cA2 as adjunctive and/or concomitant therapy to methotrexate therapy is an important and efficacious therapeutic approach for treating RA in patients.

In contrast to applicant's assertions with respect to Example 1; pages 62-63, overlapping paragraph of the instant specification discloses that: the results of the study indicate that treatment with a multiple dose regimen of cA2 as adjunctive and/or concomitant therapy to methotrexate therapy, in RA patients whose disease is incompletely controlled by methotrexate, produces a highly beneficial or synergistic clinical response that can be sustained through 26 weeks. The benefit produced by cA2 generally exceed 50% reduction in the traditional measurement of rheumatoid arthritis (swollen and tender joints, patient and physician global diseases assessments) and achieve near clinical remission in many patients. Accordingly, the results of this study indicate that treatment with multiple infusions of cA2 as adjunctive and/or concomitant therapy to methotrexate therapy is an important and efficacious therapeutic approach for treating RA in patients.

In contrast to applicant's arguments that nothing in the record would indicate that the ordinary artisan would reasonably conclude a dramatic effect would be expected by combination therapy with methotrexate and anti-TNFα antibody; applicant is invited to consider the combination of references cited in the New Grounds of Rejection below.

10. Claims 13 and 5--31 are rejected under 35 U.S.C. § 103 as being unpatentable over Le et al. (U.S. Patent No. 5,656,272) and Aggarwal et al. (U.S. Patent No. 5,672,347) in view of Barrera et al. (Cytokine, 1991) and Kozarek et al. (Ann. Int. Med., 1989) of Markowitz et al. (J Ped. Gastroenterology and Nutrition, 1991), Brahn et al. (Arthritis Rheum, 1992); Cohen et al. (Rev. Esp. Rheumatol., 20 Suppl 1:148 (1993), Abstract 318; see 1449, #AR3), Pascalis et al. (Rev. Esp. Rheumatol., 20 Suppl 1:148 (1993), Abstract 319; see 1449, #AR3).

The instant claims are drawn to methods and compositions comprising methotrexate and TNF-specific antibodies.

Le et al. teach the use of TNF-specific antagonists including the instant cA2 antibody to treat inflammatory diseases including arthritis, Crohn's pathology and ulcerative colitis (see entire document, including Therapeutic Administration in columns 35-38, Examples XX-XXIII in columns 58-79). It is noted that the clinical patients targeted by the cA2 treatment in the clinical trials taught by Le et al. were refractory to disease modifying anti-rheumatic drugs (DMARD); however it is also noted that methotrexate was such a DMARD (see Example XXII for example). Even though the particular patient populations employed in the referenced clinical trials were refractory to standard DMARD including methotrexate treatment, it would have been obvious to the ordinary artisan that the combination of standard methotrexate treatment in combination with a highly effective TNF antagonist such as cA2 would be similarly effective for treating patients with inflammatory conditions already being treated with standard methotrexate as well as a TNF antagonist. Also, Le et al. teaches that the anti-TNF peptides and/or mAbs of their invention can be administered either as individual therapeutic agents of in combination with other therapeutic agents (see column 35, lines 25-32).

Aggarwal et al. teaches the use of TNF antagonists including TNF-α-specific antibodies and analogues to treat various inflammatory conditions including arthritis and Crohn's disease (see entire document, including overlapping paragraph of columns 6-7). Aggarwal et al. also teach that the TNF antagonist can be administered in conjunction with other anti-inflammatory agents used in or prosed for the treatment of individual immmunoinflammatory conditions as appropriate (column 7, lines 60-67). Here, TNF antagonists when employed together with other anti-inflammatory agents, these agents may be employed in lesser dosages than when used alone. Although this reference does not teach the particular cA2 specificity per se, Aggarwal et al. clearly teaches the use of TNF-α antagonist to treat inflammatory conditions encompassed by the claimed invention. In addition, Aggrarwal et al. teaches the art known advantages of combination therapy, wherein the ordinary artisan can take advantage of two or more therapeutic agents to treat the same disease and that in instances, this combination permits one agent to be used in lesser amounts, thereby counteracting any toxic effects,

Barrera et al. teaches the use of methotrexate including suppressing the production of TNF in arthritic patients (see Abstract).

Cohen et al. and Pascalis et al. teach the use of methotrexate to treat refractory rheumatoid arthritis.

Kozarek et al. teach the use of methotrexate as an anti-inflammatory agent on inflammatory bowel disease (see entire document).

Markowitz et al. teaches targeting TNF (page 413) and the use of methotrexate (page 421) in the treatment of inflammatory bowel diseases (see entire document)

Therefore, the prior art taught the claimed TNF-specific antagonists and methotrexate as well as their combinations; therefore it would have been obvious to one of ordinary skill at the time the invention was made to make various combinations of said anti-inflammatory antagonists to achieve the same desired goals in treating arthritis and Crohn's disease. diminished TNF activity to suit the nature of the therapeutic regimen. The combination of references provide an expectation of success in combining various compositions to form a third composition to most effectively induce the appropriate immunosuppression for a targeted condition.

One of ordinary skill in the art at the time the invention was made would have been motivated to combine targeting the different elements contributing to inflammatory responses including those associated with arthritis and Crohn's disease. The art teaches that targeting TNF can all diminish the activity of inflammatory responses, including the use of either TNF-specific agents such as TNF-specific chimeric antibodies or an anti-inflammatory agent such as methotrexate. Combination therapies were well known in the art and both methotrexate and anti-TNF antibodies were shown to be effective in vivo. It was prima facie obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

11. The non-statutory double patenting rejection, whether of the obvious-type or non-obvious-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (b) and © may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78 (d).

Effective January 1, 1994, a registered attorney or agent of record may sign a Terminal Disclaimer. A Terminal Disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. Claims 1-3 and 5-31 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 15-30 of copending application Serial No 08/607,419 in view of the art recognized use of immunosuppressive therapy encompassing cyclosporin and methotrexate in arthritis and Crohn's diseases and xanthine derivatives in the treatment or reduction of TNF-mediated diseases, as set above in section 12. For example, Markowitz et al.(J Ped. Gastroenterology and Nutrition, 1991) discloses teaches targeting TNF (page 413) and the use of cyclosporin and methotrexate (page 418-421) in the treatment of inflammatory bowel diseases (see entire document). For example, Cohen et al. (Rev. Esp. Rheumatol., 20 Suppl 1:148 (1993); see 1449, #AR3); Abstract 318 and Pascalis et al. (Rev. Esp. Rheumatol., 20 Suppl 1:148 (1993); Abstract 319; see 1449, #AR3) discloses the use of cyclosporin and methotrexate to treat refractory rheumatoid arthritis. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are drawn to same or similar methods to treat inflammation, including arthritis and IBD for the reasons above.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

13. Claims 1-3 and 5-31 are directed to an invention not patentably distinct from claims 15-30 of commonly assigned USSN 08/607,419 because the claims are drawn to same or similar methods to treat inflammation, including arthritis and IBD, with combination therapy encompassing TNF-specific inhibitors with art-recognized therapeutic regimens for the reasons above.

Commonly assigned 08/607,419, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. § 103 if the commonly assigned case qualifies as prior art under 35 U.S.C. § 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 37 C.F.R. § 1.78© to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application. A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. § 103 based upon the commonly assigned case as a reference under 35 U.S.C. § 102(f) or (g).

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee can be reached on (703) 308-2731. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1800 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014 or (703) 308-4242.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to **[lila.feisee@uspto.gov]**.

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Phillip Gambel, Ph.D.
Patent Examiner
Group 1800
December 8, 1997